REMARKS

I. Introduction

This is in response to the Office Action dated July 25, 1995. Submitted herewith is a petition under 37 CFR §1.136 and the required fee requesting a three month extension in which to file this amendment. With the extension, this response is due on January 25, 1996. No additional fees are believed to be necessary for the filing of this amendment, but if such fees are required, applicants request that this be considered a petition therefor, and the Commissioner is hereby authorized to charge any additional fees which may be required for the filing of this amendment to Deposit Account No. 11-1158.

The requirement for formal photographs and for a petition under 37 CFR 1.84(b) is noted. Such a petition will be submitted once allowable subject matter has been agreed upon, if not sooner. Replacement photographs will be submitted when such a petition has been granted, if not sooner.

II. Title

As requested by the Examiner, the title of the invention has been amended in order to clearly indicate that the invention to which the claims are directed involves "the use of antibodies specific to human complement component

C5". Support for this change may be found on page 1, line 10 of applicants' specification.

III. The §112 ¶1 Rejections

The Examiner has objected to the specification and rejected claims 1-6 under 35 U.S.C. §112, first paragraph, for "insufficient evidence or nexus with respect to in vivo operability of C5-specific antibodies". Applicants are puzzled by the Examiner's assertion that Examples 1-4 disclose extracorporeal treatment only. While Examples 1-4 of copending US patent application Serial No. 08/217,391, filed March 23, 1994, which is cited in the instant specification, do disclose extracorporeal treatment only, examples 1-3 of the instant application disclose only *in vivo* treatment, and examples 4-6 disclose both *in* vivo and extracorporeal treatment data. Clarification is respectfully requested.

The Examiner asserts that pharmaceutical therapies in the absence of *in vivo* clinical data are unpredictable. Applicants respectfully note that the U.S. Court of Appeals, Federal Circuit, has recently ruled in regards to a rejection of claims directed at a new drug under §112 for lack of a showing of *in vivo* human operability that such a rejection was improper, given the evidence of operability in animals, and that "[u]sefulness in patent law, and in particular in the context of pharmaceutical inventions, necessarily includes the expectation of further research and development. The stage at which an invention in this field

becomes useful is well before it is ready to be administered to humans." *In re Brana*, 34 USPQ2d 1438, 1442 (Fed. Cir. 1995).

Applicants note in this regard that they have provided evidence of *in vivo* operability in a mouse model of glomerulonephritis in their specification. Nonetheless, a "Declaration of Scott Rollins Pursuant to 37 C.F.R. §1.132", and a "Declaration of Louis Matis Pursuant to 37 C.F.R. §1.132", each of which sets forth, *inter alia*, experimental data that further demonstrate the operability of applicants' invention, are being prepared and will be submitted shortly.

In addition, with regard to the pharmacokinetics of monoclonal antibodies in general, the Harris et al. reference cited by the Examiner (Examiner's reference R1) indicates at page 42, column 3, that murine antibodies generally have *in vivo* half-lives on the order of 15 hours, and that chimeric antibodies have even longer half-lives *in vivo*, on the order of 100 hours. In addition, rodent monoclonal antibodies in general have been shown to be non-toxic in clinical use, and Harris et al. state that "an important conclusion, drawn from all the available data, is that chimaeric antibodies are non-toxic." (Harris et al., p. 42, column 3).

The Examiner has disparaged antibody therapy based on the Harris et al. reference. The key assertion by Harris et al. cited by the examiner in this regard is that repeated dosing with chimeric antibodies is ineffective due to anti-

idiotypic responses. This assertion is belied by the actual *in* vivo human data currently available, as exemplified by the recent FDA approval and successful marketing of the chimeric monoclonal antibody antithrombotic agent REOPRO, which, unlike the other currently marketed monoclonal antibody, OKT3, is not an immunosuppressive agent and is not typically used in immunosuppressed patients. Further *in vivo* human experimental evidence demonstrating the utility of monoclonal antibody therapy will be presented in a "Declaration of Stephen P. Squinto Pursuant to 37 C.F.R. §1.132", which is being prepared and will be submitted shortly.

The Examiner also avers that

> [t]he specification does not adequately teach how to effectively inhibit the disease/treatment endpoint in humans by administering an inhibiting monoclonal antibody. The specification does not teach how to extrapolate data obtained from these controlled conditions evaluating extracorporeal treatment with C5/C5b-specific antibodies to the development of effective in vivo human therapeutic methods which are directed toward a chronic ongoing disease.

In fact, the procedures for administering the therapeutic proteins used in the process of the invention and monitoring their effects are fully set forth in applicants' specification (see, for example, pages 25-28). The Rollins and Matis Declarations discussed above (which will be submitted shortly) will provide further support for applicants' contention that standard procedures well known

in the art are all that are required for the actual practice of the invention.

Furthermore, the guidance for the development of effective in vivo human therapeutic methods provided in applicants' specification is not limited to the controlled conditions evaluating extracorporeal treatment mentioned by the Examiner. As discussed above, applicants' specification also provides working examples demonstrating the practice of their invention via effective *in vivo* therapeutic methods in a widely used animal model of glomerulonephritis.

The above discussions will be extended by the Matis and Rollins Declarations in preparation, which will present further support for the need for only routine and conventional experimentation to successfully practice the claimed methods of the instant application.

The Examiner has also asserted that it is unclear whether the antibodies used in the practice of the invention would be neutralized by the patient's complement found in the circulation. The *in vivo* data of the specification, as well as data to be submitted in the Rollins and Matis declarations discussed above, clearly show that if any such neutralization does occur, it is not sufficient to render the methods of the invention inoperative.

With regard to therapeutic complement inhibitors in general, the Examiner has cited Liszewski et al. (Examiner's reference S3), Morgan (Examiner's reference S4), and Kalli

et al. (Examiner's reference T5). It appears that the Examiner's discussion of these references is colored by the misapprehension that no *in vivo* evidence of operability is presented in applicants' specification. As discussed above, this is not the case.

In the Examiner's argument contending that applicants' claims are not adequately enabled by their specification, Morgan (Examiner's reference S4) is cited as indicating that long term complement inhibition could leave the recipient susceptible to infections (see Morgan, p. 225 column 1, final paragraph). In this regard, applicants draw the Examiner's attention to the sentence immediately following the cited sentence in the referenced paragraph, which reads: "These problems pose a challenge to clinicians, but are unlikely to restrict our use of these exciting new agents."

Morgan's comments regarding infections are made in the context of his discussion of sCR1 in the preceding sentences of the referenced paragraph. As discussed at page 12, line 23, to page 13, line 8 of applicants' specification, lack of C3 function (as occurs with sCR1 treatment) leaves patients prone to a broad variety of infections, while lack of C5 function (as occurs in association with the practice of the present invention) only has a minor effect on susceptibility to infection, and then only to Neisseria infection. This represents a distinct advantage of applicants' invention

over prior art approaches to therapeutic complement inhibition.

Applicants believe that the preceding discussion fully addresses the Examiner's concerns, and respectfully request that the Examiner reconsider and withdraw his rejections under §112, paragraph 1.

IV. <u>The §112 ¶2 Rejections</u>

The Examiner has rejected claims 1-8 under 35 U.S.C. §112, second paragraph, as being indefinite for a combination of reasons including (A) indefiniteness in the recitation of an antibody that "binds to" and an antibody "to" (claims 1-8); (B) indefiniteness "in the recitation of a 'pharmaceutical agent' because it is unclear whether applicant is claiming a compound or composition" (claims 6-9); and (D) duplicative claiming (claims 7-9).

Regarding reason (A), claim 1 has been amended in accordance with the Examiner's suggestion to recite an antibody " specific to" C5. Support for this change can be found at page 1, line 10 of applicants' specification. Claims 2-5 depend on Claim 1, and are thus also corrected by the language of this amendment.

Regarding reason (B), claims 6-9 recite an "article of manufacture" and thus are directed neither at a compound nor a composition *per se*, but at a "manufacture" in accordance with 35 U.S.C. §101. Applicants respectfully traverse the Examiner's assertion that the claims read on a composition

per se. Nonetheless, in the interest of expediting prosecution, applicants have hereby canceled claims 6-9 without prejudice to their use in a continuing application.

Regarding reason (C), as discussed in the preceding paragraph, claims 6-9 were directed to <u>articles of manufacture</u>, not compositions. The articles of manufacture of claims 6-9 comprise combinations of packaging materials and formulations, and are distinguished from each other by the indicia of the label portion of the packaging material. Applicants therefore respectfully traverse the Examiner's assertion that claims 7 and 8 are essentially duplicative of claim 6.

Applicants believe that the preceding discussion fully addresses the Examiner's concerns, and respectfully request that the Examiner reconsider and withdraw his rejections under §112, paragraph 2.

V. <u>The §103 Rejections</u>

In the July 25th Office Action, the Examiner rejected applicant's pending claims 1-5 under 35 U.S.C. §103 over Wurzner et al. (Complement Inflamm., 1991; 1449 #20) in view of Couser et al. (J. AM. Soc. Nephrol., 1991, 1449 #5) and Sims et al. (U.S. Patent No. 5,135,916 1449 #1). Applicants respectfully traverse these rejections, as well as the rejections of claims 6-9 (hereby canceled) over Wurzner et al. (Complement Inflamm., 1991; 1449 #20).

Applicants' traversal of these rejections is based upon several arguments, including the following:

1. As discussed in applicants' specification, page 23, lines 6-16, it would be counterintuitive to treat a disease process that involves inordinately high levels of circulating antibody-antigen immune complexes, resulting in immune complex deposition in the kidney, with a treatment that is almost certain to result in the generation of more circulating antibody-antigen immune complexes, and this increase the already pathologically high levels of such complexes in the circulation. Furthermore, Kalli et al. (Examiner's reference T5) and Harris et al. (Examiner's reference R1) teach away from applicants' invention.

2. Even if it were obvious to try (and argument 1, above, demonstrates that it would not be) a practitioner of ordinary skill in the art would not have had a reasonable expectation of success, both due to the reasons discussed in argument 1, above, and because of other reasons arising from the level of understanding in the art at the time the invention was made. For example, the prior art would have suggested that complement inhibition alone, while useful for preventing the onset of inflammation in which complement activation played a role, would not be effective in treating such inflammation once the inflammatory process was underway.

3. Given the level of understanding in the art at the time the invention was made, and in particular, in comparison to the closest available prior art (particularly Couser et al., (J. AM. Soc. Nephrol., 1991, 1449 #5) the results obtained from the practice of the present invention were unexpected and surprising.

4. There has been a long felt but unsolved need in the art for methods such as those of the present invention. See Liszewski et al. (Examiner's reference S3, first full paragraph of page 933) "Because complement can mediate cell and tissue damage in autoimmune syndromes, the possibility of harnessing its inhibitors to prevent undesirable activation has been a longstanding goal. At the present time there are no inhibitors of complement activation utilized in clinical medicine." In this regard, applicants note that the all of the references cited by the Examiner were published in 1991. Thus, several years elapsed between the time that these references became available and the filing date of the instant application, during which time, and in spite of the long felt and unsolved need in the art, no other practitioners used antibodies against C5 (or any other terminal complement component) as therapeutic agents for the treatment of kidney disease.

Declarations are currently being prepared that will provide additional support for applicants' contention that

the instant invention is nonobviousness. These declarations will be submitted shortly, along with a supplemental amendment that will provide a more extensive discussion of applicants' arguments for the nonobviousness of their invention.

In sum, applicants believe that their amended claims fully satisfy the requirements of section 103 of the Patent Statute. Applicants therefore respectfully request that the Examiner reconsider and withdraw his rejections under §103.

VI. Conclusion

In view of the foregoing, applicants respectfully submit that the present application is in condition for allowance. Accordingly, reconsideration and the issuance of a notice of allowance for this application are respectfully requested.

Respectfully submitted,

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